Endemic Mycosis Complicating Human Immunodeficiency Virus Infection

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Persons infected with the human immunodeficiency virus are prone to the development of many fungal diseases. Normal hosts with intact immunity usually recover from infection by these less-invasive fungi. In persons with compromised T-cell–mediated immunity, however, widespread dissemination from a pulmonary focus occurs. In this review, we discuss the epidemiology, clinical manifestations, diagnosis, and treatment of the three major North American mycoses, histoplasmosis, blastomycosis, and coccidioidomycosis. In most cases, amphotericin B is the initial drug of choice, followed by one of the azoles for lifelong maintenance therapy.

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Among many thousands of fungi existing in nature, fewer than 100 have been associated with human illness. Most of these cause disease only on the skin because this organ, with its large surface area, has the greatest environmental contact with these organisms. The second great contact between humans and the environment are the lungs. A large number of fungal spores are inhaled daily, but clinical illness produced by these organisms is uncommon.

Fungal diseases can be divided into two broad groups: diseases caused by normally pathogenic fungi, and a second group caused by fungi of lesser invasiveness that produce disease only in hosts whose immune defenses have been compromised. The pathogenic fungi include the four major endemic mycoses, histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis, that cause disease in their respective endemic areas. Cryptococcosis, the fifth major pathogenic fungal disease, is distributed worldwide. Other fungal diseases have recently come to medical attention, but their relative rarity and their poorly understood ecologic niche prevent a more thorough discussion at this time. Such a fungus is *Penicillium marneffei*, recently described in Thailand and other countries in Southeast Asia.

The endemic mycoses share a single important feature. If their infecting particles are not cleared by nonspecific host defenses, they convert to an invasive or tissue phase that is resistant to killing by nonimmune phagocytes, both neutrophils (polymorphonuclear [PMN]) and macrophages.[1] In the United States, histoplasmosis,[2] blastomycosis,[3] and coccidioidomycosis[4,5] are common, whereas paracoccidioidomycosis exists exclusively in South and Central America and will not be discussed further.[6]

These endemic mycoses cause infection in any nonimmune host; the eventual control and elimination of the fungi require the development of specific T-cell–mediated immunity. Normal hosts with intact T-cell–mediated immunity usually recover from primary infection by any of these fungi, unless the infecting dose is overwhelming.[3-8]

Opportunistic invasive fungal infections, which include aspergillosis, pseudallescheriasis, and mucormycosis, are caused by fungi that are ubiquitous in nature. Unlike spores of normally pathogenic fungi that cannot be killed by nonimmune phagocytosis, inhaled spores of the opportunistic fungi are easily dealt with by PMNs and alveolar macrophages.[1] Progressive infection by these fungi takes place only when the number or function of these phagocytes is impaired.[9,10] Although disturbances of T-cell–mediated immunity also play a role in allowing systemic infections to occur, these infections are rare even in patients with profoundly altered T-cell–mediated immunity, unless there is a concomitant alteration in the number or function of PMNs and macrophages.[11] Thus, invasive disease produced by these fungi seldom develops in patients infected with the human immunodeficiency virus (HIV).[12] Most HIV-infected patients in whom invasive aspergillosis develops have substantial alterations in PMN number and function, although a few patients have been described who have no obvious phagocyte defect.[13] Diseases caused by these organisms will not be dealt with in this article, nor will we discuss infection with *Candida* species. Mucosal infection with *Candida* species (controlled by T-cell–mediated immunity) is extremely

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
BAL = bronchoalveolar lavage
CF = complement fixation
HIV = human immunodeficiency virus
HPA = histoplasma polysaccharide antigen
PMN = polymorphonuclear neutrophil

common in patients with the acquired immunodeficiency syndrome (AIDS), but deep invasion (controlled by phagocytes) is remarkably uncommon.

The three major endemic mycoses of North America, histoplasmosis, blastomycosis, and coccidioidomycosis, share a number of features. All are soil organisms; human infection occurs when the fungal spores are inhaled. For the vast majority of patients, the portal of entry is the lungs. All three organisms are dimorphic. They grow in nature as hyphae, and the infecting spores are small, ideally sized to reach the terminal alveoli. *Histoplasma capsulatum* and *Blastomyces dermatitidis* are thermal dimorphs. After entering a mammalian host with an average body temperature of 37°C (98.6°F), the inhaled spores promptly convert to their tissue-invasive phase, which are single budding yeasts. *Coccidioidomyces immitis* is also a dimorphic organism, but in this instance the invasive phase is a giant spherule, rather than a single budding yeast. The change of form is not mediated by temperature alone, and the organism is sometimes called a tissue dimorph.

The primary pulmonary infection of these fungi in nonimmunocompromised hosts is usually a self-limited disease. Only when specific T-cell–mediated immunity is depressed do these organisms become highly invasive, resulting in widespread dissemination from a pulmonary focus.

The endemic mycoses exist in well-defined geographic areas. Histoplasmosis exists in the south-central United States, especially along major rivers.[2] Blastomycosis is coendemic over most of this area, but extends further north to include Wisconsin, Minnesota, and adjacent Canadian provinces.[3] This organism also is concentrated along waterways. Coccidioidomycosis is endemic in the desert Southwest, roughly corresponding to the area of the Lower Sonoran Life Zone. This area, as high as 1,067 m (3,500 ft) elevation, is the home of the fungus. Geographically this area encompasses west Texas, parts of New Mexico, the desert part of Arizona, and the southern part of the Central Valley of California. In addition, adjacent areas of northern Mexico are also highly endemic.[4,5]

The histopathology of the primary infection is different among the various fungi. The histopathology of histoplasmosis is primarily granulomatous, without a PMN infiltrate.[7] Primary lesions of blastomycosis and coccidioidomycosis are usually pyogranulomatous. In addition to granulomas, PMNs persist in greater or lesser numbers during active infection.[3-5]

Histoplasmosis in the Acquired Immunodeficiency Syndrome

Following the inhalation of the infecting spores, an area of pneumonitis develops, usually in the better-ventilated lower zones of the lung. During the preimmune phase of the infection, the organism gains access to the circulation through the lymphatics and disseminates widely throughout the body, where it is taken up by cells of the reticuloendothelial system. With the development of cell-mediated immunity, the now "armed" macrophages are able to kill the ingested fungi, leading to the production of granulomas and eventually healing by fibrosis.[7] It is easy to understand why in patients whose T-cell–mediated immunity has been altered by HIV infection, progressive dissemination by *H capsulatum* is especially prone to develop.

The primary infection in normal hosts is usually a self-limited illness. The acute phase of the illness frequently presents with influenza-like symptoms, but the patient recovers quickly. Sputum production is uncommon, and the vast majority of infected persons never come to medical attention due to rapid spontaneous recovery. In patients with far-advanced HIV infection, unchecked progressive dissemination takes place that may kill the host.

Progressive Disseminated Histoplasmosis

Progressive disseminated histoplasmosis may take two different forms. In adults with immunosuppression not due to AIDS and young children, there is poor granuloma formation in response to the infection.[14] The organism rapidly proliferates. This form of the disease mimics lepromatous leprosy. Because of its propensity to infect young children, this form of disseminated histoplasmosis has been referred to as the "infantile" form of the disease. In older patients, progressive disseminated histoplasmosis is a disease with a much slower pace; granulomas are well formed throughout, and only a rare organism may be seen.[14] This form of the disease has been compared with the tuberculous form of leprosy. Even before the onset of the HIV pandemic, the infantile form of progressive disseminated histoplasmosis was seen almost exclusively in immunologically altered patients, especially in persons receiving high-dose glucocorticoids or immunosuppressive therapy by cytotoxic agents.[15,16] The pace of the disease is rapid due to the unchecked proliferation of a large number of histoplasma yeasts.

Progressive disseminated histoplasmosis was reported in HIV-infected patients as early as 1981,[17] but it was not until 1987, following the reports of an increasing number of cases of the disease in HIV-infected patients, that it was accepted as an AIDS-defining illness.[18] Clinically and histopathologically, progressive disseminated histoplasmosis in patients with AIDS resembles the infantile form of the disease.

Progressive Disseminated Histoplasmosis in the Acquired Immunodeficiency Syndrome

Epidemiology

Unlike the primary form of histoplasmosis, which occurs either sporadically or in point-source outbreaks in the recognized endemic area, progressive disseminated histoplasmosis in AIDS has been described both within the endemic area and with increasing frequency outside the endemic area. Early reports first drew attention to the association of HIV infection with this disease in heavily endemic parts of the United States.[19,20] Shortly after, however, a number of reports appeared in the literature describing cases of the disease in areas of the United States not considered endemic. Careful epidemiologic investigation of the involved patients revealed that all had previously resided in areas known to be endemic for histoplasmosis.[21] On the East Coast of the United States, most patients with progressive disseminated histoplasmosis and AIDS had previously resided in Puerto Rico and other Caribbean islands, whereas on the West Coast, most had resided previously in the Midwest and south-central United States. The incidence of the disease in AIDS is highly variable from location to location. From series described from Dallas[22] and Houston,[23] on the fringes of the recognized endemic area, the dual infection occurs in about 5% of patients known to have AIDS. In more heavily endemic areas of the United States, such as Indianapolis, Indiana, progressive disseminated histoplasmosis has developed in a much larger percentage of AIDS patients. In one report, the disease was described in 27% of such patients.[24] By comparison, cryptococcal meningitis involves 6% to 10% of AIDS patients throughout the United States.[25]

Pathophysiology

The ongoing epidemic of histoplasmosis in Indianapolis has shown that when HIV-infected patients come in contact with the fungus for the first time, widespread disseminated disease will occur.[24] On the other hand, patients with disseminated histoplasmosis diagnosed in nonendemic areas who uniformly give a past history of residence in endemic areas likely are reactivating latent disease from remote exposure.[21] Further supporting the concept of endogenous reactivation in these patients is that in many the chest radiograph is normal during the initial presentation of the disease.[26]

Clinical Manifestations

The clinical presentation of progressive disseminated histoplasmosis complicating AIDS is nonspecific. It is similar to many other opportunistic infections complicating the course of HIV infection. In published reviews of the disease in patients with AIDS, fever and weight loss were the most common symptoms, occurring in about 75% of patients.[24,26] Physical examination is frequently unrevealing, although hepatosplenomegaly may occur in as much as 25% of patients.[24,26] Lymphadenopathy may occur in a small fraction. Routine laboratory test results are also nonspecific, although many patients show anemia, leukopenia, and thrombocytopenia. All of these cytopenias are frequently seen in patients receiving zidovudine therapy. The chest radiograph at presentation may range from normal to diffuse reticulonodular infiltrates.[26] Ultimately, virtually all patients show a diffuse reticulonodular picture. Respiratory symptoms, such as cough and dyspnea, are far more likely to occur in patients with diffuse infiltrate. Uncommon sites of involvement include gastrointestinal ulcers,[27] intracerebral lesions and meningitis,[28] and skin ulcers.[26] In patients whose illness is rapidly progressive, the features of disseminated intravascular coagulation have been recognized. This latter manifestation tends to carry an extremely poor prognosis.[24]

Diagnosis

A prompt diagnosis requires a high degree of suspicion. The goal is to identify the infecting organism quickly from biologic material. The organisms may be seen circulating in peripheral blood within phagocytes. The peripheral blood smear should be diligently searched in all febrile AIDS patients.[29] When looked for, the characteristic intracellular yeast can be found in close to half the patients. In one series, 12 of 26 patients had recognizable yeasts of *H capsulatum* in peripheral blood, and in an astonishing 10 of 12, the peripheral blood film was the first hint of the fungal cause of the febrile illness.[22] The organism is readily recovered from blood cultures, especially when the lysis centrifugation technique is used. In a series from Indiana University Hospitals, the blood culture was positive in 91% of the patients whose progressive disseminated histoplasmosis complicated AIDS.[24] Even though the blood culture is frequently positive, perhaps the most rapid and sensitive test available is the examination of the bone marrow.[16,23] The organisms are readily seen in macrophages with the use of either a silver stain or by the periodic acid–Schiff stain. The advantage of the bone marrow examination is its simplicity. The diagnosis can usually be established within hours after doing a bone marrow biopsy. The organism may also be recognized in bronchoalveolar lavage (BAL) specimens[21] and in histopathologic sections prepared from biopsies of skin, lymph nodes, or other tissues.

Serologic testing is frequently extremely helpful. The immunodiffusion and complement fixation (CF) tests are frequently positive; when used together, these serologic tests will identify about 80% of involved patients.[24] The main drawbacks to the use of these serologic tests are poor sensitivity early in the illness, poor sensitivity in the most severely immunosuppressed, and a long turnaround time. The best single serologic test is measurement of the histoplasma polysaccharide antigen (HPA) level by radioimmunoassay.* In one series, the

*The test is performed by the Histoplasmosis Reference Laboratory, 1001 W 10th St, OPW441, Indianapolis, IN 46202-2879; phone 1-800-HISTO-DG.

test was positive in the urine of 70 of 72 HIV-infected patients with disseminated histoplasmosis.[30] This test is useful both for diagnosis and for monitoring treatment response and early relapse.[31] The measurement of HPA is extremely valuable in AIDS patients with this disease because the burden of organisms is so high. The test is not as useful in other forms of histoplasmosis, especially in more immunocompetent hosts.

Treatment

Similar to many other opportunistic infections complicating AIDS, progressive disseminated histoplasmosis cannot be "cured." Following the successful initial induction of treatment, lifelong suppressive therapy is needed. The incidence of relapse is unacceptably high in patients who do not receive long-term suppressive therapy. This was clearly established early during the epidemic, when upward of 50% of patients suffered a relapse after an initially successful treatment course.[26]

The mainstay of therapy for the disease in patients with AIDS is still amphotericin B. Although the exact dose required for stabilizing a patient is unknown, most agree that an initial induction course of between 500 and 1,000 mg should be given until a patient is clinically stable.[24,26] This, then, can be followed by itraconazole, 200 mg twice a day for the life of the patient.[32] Recent information shows that stable patients with progressive disseminated histoplasmosis complicating AIDS may be treated safely with itraconazole as primary therapy. These patients should receive the drug in a dose of 200 mg twice a day for life.[33] Fluconazole has also been tried for long-term maintenance, but it is not as effective as itraconazole.

Blastomycosis

Blastomycosis is an uncommon disease even in its endemic area. Blastomycosis complicating AIDS is an extremely uncommon infection, with only one large series[34] and occasional additional cases reported in the literature.

Epidemiology and Pathogenesis

Because of the small number of cases described, it is difficult to discuss the epidemiology. Whereas many cases of dual infection (HIV and blastomycosis) were reported from areas known to be endemic for the fungus, a number of patients were seen in areas normally considered outside the endemic zone.[34] Although it is possible that some patients recognized outside the endemic area were incubating their primary infection before the development of overt clinical illness, many had been away from all possible contact with the endemic area for several years. Thus, it is likely that HIV-infected patients may reactivate previously dormant foci of blastomycosis once T-cell–mediated immunity fails.

Clinical Manifestations

The spectrum of disease of blastomycosis is variable. It ranges from an indolent, slowly progressive pulmonary disease to a rapidly disseminating and fatal illness involving many organs. The lungs are usually involved. Radiographic manifestations of the disease are variable, ranging from segmental or lobar infiltrates to a large number of moderately sized pulmonary nodules. In a few patients with rapidly progressive and widely disseminated disease, the radiograph shows rapidly evolving reticulonodular infiltrates, indistinguishable from progressive disseminated histoplasmosis or *Pneumocystis carinii* pneumonia. Fulminant interstitial and miliary disease may also be seen, which has on occasion progressed to the adult respiratory disease syndrome. Central nervous system involvement is common and is usually symptomatic.[34]

Diagnosis

The standard of diagnosis is cultural recovery of the fungus from biologic material, but this is usually time-consuming. Direct visualization of the organism (a characteristic large yeast with a single broad-necked bud) from biologic material, such as BAL fluid, or histopathologic examination of biopsy material is faster. The single best test for diagnosis is the microscopic examination of respiratory specimens after 10% potassium hydroxide digestion.[3] In digested specimens, other components of the sputum are dissolved, leaving the characteristic yeast visible. Good results may also be obtained by staining respiratory specimens with the Papanicolaou stain.[35] Standard serologic tests are not considered reliable enough. When positive, they help to focus the search for *B dermatitidis*.[36] There is no commercially available skin test.

Treatment

The mainstay of the treatment of patients with blastomycosis and AIDS is still amphotericin B. The drug should be used in all patients where the pace of the disease is rapid and where there is evidence of central nervous system involvement.[34] In this subset of patients, primary therapy with azoles is inappropriate. The exact dose needed for the stabilization of a patient with blastomycosis and AIDS is not established. Most agree that as much as 2 grams of the drug should be delivered. Following clinical stabilization, the patient is then placed on a regimen of itraconazole, 200 mg twice a day, which should be maintained for the duration of the patient's life.[34,37] Although suppressive therapy with itraconazole is successful in nonmeningeal disease, it is unclear whether central nervous system blastomycosis can be successfully suppressed with oral azoles. The role of fluconazole is considered uncertain in this illness.[38]

Coccidioidomycosis

Epidemiology

Cases of coccidioidomycosis complicating AIDS have been described with increasing frequency from the endemic areas of the United States. Although this combination of infections was a latecomer to opportunistic infections complicating HIV infection, it has now

assumed increasing frequency as the epidemic has moved inland from the West Coast.[39] In the large urban centers of Arizona, for example, coccidioidomycosis is now the third most frequently reported opportunistic infection complicating AIDS.[40]

The study of coccidioidomycosis is unique among the endemic mycoses because of the performance of a carefully conducted prospective study in the Tucson-Phoenix metropolitan area. In this study, 170 HIV-infected patients were observed from the diagnosis of HIV disease. The study has shown that active coccidioidomycosis frequently develops among HIV-infected patients living in the endemic area. By the end of 3½ years of follow-up, about 25% of the patients had active disease. For most patients in whom active coccidioidomycosis developed, the disease was the result of primary infection. For at least two patients, however, the disease was due to reactivation. These two patients had a positive coccidioidin skin test on enrollment in the study, and in both, severe progressive coccidioidomycosis developed during the period of observation.[40]

Pathophysiology

From the above-mentioned large cohort study, it appears that with decreasing T-cell–mediated immunity, the risk of acquiring a progressive infection increases. The major risk for the development of progressive coccidioidomycosis was a CD4 count of less than 250×10^9 per liter. Surprisingly, the length of residency in the endemic area was not correlated with the development of active disease.[39,40]

Clinical Manifestations

The clinical manifestation of coccidioidal infection occurring among HIV-infected patients depends on a patient's CD4 count at the time of diagnosis. In patients with normal or near-normal CD4 counts, the infection resembles the disease seen in immunologically intact persons. The infection may produce single nodules, cavities, or infiltrates that are indistinguishable from those seen in normal hosts. In most of these patients, the course of the coccidioidal infection is mild.[39]

In patients with more severe immunosuppression, active coccidioidomycosis frequently occurs as a fulminant respiratory infection. Symptoms are fever, weight loss, and cough productive of mucopurulent sputum.[39,40]

Coccidioidomycotic meningitis is fairly common. In a large series reported from Phoenix, 14 of 91 patients with AIDS and coccidioidomycosis had meningitis.[41] Symptoms are variable, ranging from minimal alterations in the level of cognition to the rapid development of coma. Whereas in many patients the chest radiograph is abnormal, in some patients the sole manifestation of the infection is meningitis. In the endemic area, the diagnostic suspicion must be great to facilitate timely diagnosis. Early lumbar puncture should be considered in all patients in the high-risk group who present with even minimal alteration in cognition.

The chest radiograph is highly variable. Among patients without severe immunocompromise, the radiographic picture of coccidioidomycosis is similar to that seen in a normal host. In patients with more severely impaired immunity, the characteristic pattern is either a diffuse macronodular infiltrate or a diffuse reticulonodular infiltrate, indistinguishable from *P carinii* pneumonia or progressive disseminated histoplasmosis. Survival among patients with the severe form of pulmonary disease has been poor.[39-41]

Diagnosis

Diagnosis requires a high degree of suspicion, especially in patients coming to medical attention outside the endemic area. Physicians caring for HIV-infected patients must obtain a careful travel history so as not to miss regionally acquired diseases far removed from their endemic area. The cornerstone of diagnosis is either cultural recovery of the organism or its visualization in respiratory secretions or histopathologic specimens. Although endospores may be seen in expectorated sputum or in respiratory secretions obtained by BAL, either by the use of 10% potassium hydroxide digestion or by the Papanicolaou technique, the diagnostic sensitivity is low and is greatly dependent on the expertise of a laboratory. In a recently completed study, cytologic identification of spherules by either technique occurred in about 40% of the proven cases.[42] Cultural recovery of the organism is more common, but requires a lengthy period of incubation. Generally speaking, when the pace of the disease is rapid and simple cytologic examination is negative, one must resort to transbronchial biopsy, and should that fail, to thoracoscopic or traditional open-lung biopsy. Diagnostic bronchoscopy often reveals large endobronchial ulcers. Biopsy of these ulcers is often positive for the organism.

Serologic testing has a major role to play in the diagnosis of coccidioidomycosis. Although standard serologic tests may not be positive, they are extremely helpful when they are positive in the appropriate patients.[40] For screening, the immunodiffusion test for both immunoglobulin M and G antibodies should be used, and when positive, the CF serologic test should be obtained. This CF test is extremely helpful and should be repeated frequently during the course of a patient's illness. In addition to its diagnostic value, the CF test is helpful in monitoring the progression of the infection. Serology is the mainstay of diagnosis in suspected cases of coccidioidomycotic meningitis because cultural recovery of the fungus is unreliable. The serologic test of choice for the diagnosis of coccidioidomycotic meningitis is the cerebrospinal fluid CF test.

Treatment

All HIV-infected patients with coccidioidomycosis should be treated, and this treatment should be maintained for the patient's life. Although exact recommendations are difficult, most experts living in the endemic area recommend amphotericin B as primary therapy for patients presenting with diffuse pulmonary infiltrates.[39,41] Due to the extremely fast pace of the disease, the more

slowly acting azoles are likely to fail. Once a patient's clinical course has stabilized on a regimen of amphotericin B, it is safe to switch to fluconazole in minimum doses of 400 mg daily. There is some experience with higher doses, but as yet, there is no proof that the higher doses are more effective. In patients presenting with focal pulmonary lesions rather than the rapidly progressive diffuse pulmonary infiltrates, fluconazole may be used as primary therapy.

Ketoconazole has been used in the treatment of the various forms of coccidioidomycosis, but its effectiveness in HIV-infected patients is difficult to evaluate. Itraconazole has also been used in some patients with coccidioidomycosis and appears to be effective in carefully selected patients.

Fluconazole treatment of coccidioidal meningitis in HIV-infected patients has been reported recently. Although most patients in the study were not HIV-infected, nine of the patients were, and their response was similar to that in the larger group. In this group, the overall response rate was 79%.[43]

The question is frequently asked whether all HIV-infected patients with a positive coccidioidin or spherulin skin test should receive therapy. Largely on the basis of the cohort study from Arizona, it appears that the risk of active disease developing is low enough that treatment is not warranted until disease becomes apparent.[40] Extreme vigilance is required, however, to monitor all such patients to recognize and treat quickly reactivated disease.

REFERENCES

1. Schaffner A, Davis CE, Schaffner T, Markert M, Douglas H, Braude AI: In vitro susceptibility of fungi to killing by neutrophil granulocytes discriminates between primary pathogenicity and opportunism. J Clin Invest 1986; 78:511-524

2. Goodwin RA Jr, Des Prez RM: Histoplasmosis. Am Rev Respir Dis 1978; 117:929-956

3. Sarosi GA, Davies SF: Blastomycosis. Am Rev Respir Dis 1979; 120:911-938

4. Drutz DJ, Catanzaro A: Coccidioidomycosis (pt I). Am Rev Respir Dis 1978; 117:559-585

5. Drutz DJ, Catanzaro A: Coccidioidomycosis (pt II). Am Rev Respir Dis 1978; 117:727-771

6. Taborda A, Arechavala AI: Paracoccidioidomycosis, *In* Sarosi GA, Davies SF (Eds): Fungal Diseases of the Lung, 2nd edition. New York, NY, Raven Press, 1993, pp 85-94

7. Goodwin RA Jr, Loyd JE, Des Prez RM: Histoplasmosis in normal hosts. Medicine (Baltimore) 1981; 60:231-266

8. Sarosi GA, Davies SF: Fungal diseases, *In* Simmons DH, Tierney DF (Eds): Current Pulmonary, Vol 13. Chicago, Ill, Mosby Year Book, 1992, pp 257-287

9. Schaffner A, Douglas H, Braude A: Selective protection against conidia by mononuclear and against mycelia by polymorphonuclear phagocytes in resistance to *Aspergillus*—Observations on these two lines of defense in vivo and in vitro with human and mouse phagocytes. J Clin Invest 1982; 69:617-631

10. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA: Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984; 100:345-351

11. Pursell KJ, Telzak EE, Armstrong D: *Aspergillus* species colonization and invasive disease in patients with AIDS. Clin Infect Dis 1992; 14:141-148

12. Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA: Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324:654-662

13. Lortholary O, Meyohas MC, DuPont B, et al: Invasive aspergillosis in patients with acquired immunodeficiency syndrome: Report of 33 cases. Am J Med 1993; 95:177-187

14. Goodwin RA Jr, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM: Disseminated histoplasmosis: Clinical and pathologic correlations. Medicine (Baltimore) 1980; 59:1-33

15. Davies SF, Khan M, Sarosi GA: Disseminated histoplasmosis in immunologically suppressed patients: Occurrence in a nonendemic area. Am J Med 1978; 64:94-100

16. Davies SF, McKenna RW, Sarosi GA: Trephine biopsy of the bone marrow in disseminated histoplasmosis. Am J Med 1979; 67:617-622

17. Centers for Disease Control (CDC): Update on acquired immunodeficiency syndrome (AIDS) among patients with hemophilia A. MMWR 1981; 31:644-652

18. CDC: Revision of the CDC surveillance case definition of acquired immunodeficiency syndrome. JAMA 1987; 258:1143-1154

19. Bonner JR, Alexander WJ, Dismukes WE, et al: Disseminated histoplasmosis in patients with the acquired immune deficiency syndrome. Arch Intern Med 1984; 144:2178-2181

20. Wheat LJ, Slama TG, Zeckel MS: Histoplasmosis in the acquired immunodeficiency syndrome. Am J Med 1985; 78:203-210

21. Salzman SH, Smith RL, Aranda CP: Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a nonendemic setting. Chest 1988; 93:916-921

22. Nightingale SD, Parks JM, Pounders SM, Burns DK, Reynolds J, Hernandez JA: Disseminated histoplasmosis in patients with AIDS. South Med J 1990; 83:624-630

23. Johnson PC, Khardori N, Najjar AF, Butt F, Mansell PW, Sarosi GA: Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1988; 85:152-158

24. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al: Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. Medicine (Baltimore) 1990; 69:361-374

25. Dismukes WE: Cryptococcal meningitis in patients with AIDS. J Infect Dis 1988; 157:624-628

26. Sarosi GA, Johnson PC: Disseminated histoplasmosis in patients infected with human immunodeficiency virus. Clin Infect Dis 1992; 14(suppl):60-67

27. Haggerty CM, Britton MC, Dorman JM, Marzoni FA Jr: Gastrointestinal histoplasmosis in suspected acquired immunodeficiency syndrome. West J Med 1985; 143:244-246

28. Anaissie E, Fainstein V, Samo T, Bodey GP, Sarosi GA: Central nervous system histoplasmosis—An unappreciated complication of the acquired immunodeficiency syndrome. Am J Med 1988; 84:215-217

29. Henochowicz S, Sahovic E, Pistole M, Rodrigues M, Macher A: Histoplasmosis diagnosed on peripheral blood smear from a patient with AIDS. JAMA 1985; 253:3148

30. Wheat LJ, Connolly-Stringfield P, Kohler RB, Frame PT, Gupta MR: *Histoplasma capsulatum* polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1989; 87:396-400

31. Wheat LJ, Connolly-Stringfield P, Blair R, Connolly K, Garringer T, Katz B: Histoplasmosis relapse in patients with AIDS: Detection using *Histoplasma capsulatum* variety *capsulatum* antigen levels. Ann Intern Med 1991; 115:936-941

32. Wheat J, Hafner R, Wulfsohn M, et al: Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome—The National Institute of Allergy and Infectious Diseases Clinical Trials and Mycoses Study Group Collaborators. Ann Intern Med 1993; 118:610-616

33. Wheat LJ, Hafner RE, Korzun AH, et al: Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Med 1995; 98:336-342

34. Pappas PG, Pottage JC, Powderly WG, et al: Blastomycosis in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1992; 116: 847-853

35. Sanders JS, Sarosi GA, Nollet DJ, et al: Exfoliative cytology in the rapid diagnosis of pulmonary blastomycosis. Chest 1977; 72:193-196

36. Davies SF: Serodiagnosis of histoplasmosis. Semin Respir Infect 1986; 1:9-15

37. Sarosi GA, Davies SF: Therapy for fungal infections. Mayo Clin Proc 1994: 69:1111-1117

38. Como JA, Dismukes WE: Oral azole drugs as systemic antifungal therapy. N Engl J Med 1994; 330:263-272

39. Fish DG, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during human immunodeficiency virus infection—A review of 77 patients. Medicine (Baltimore) 1990; 69:384-391

40. Ampel NM, Dols CL, Galgiani JN: Coccidioidomycosis during human immunodeficiency virus infection: Results of a prospective study in a coccidioidal endemic area. Am J Med 1993; 94:235-240

41. Singh VR, Smith DK, Sarosi GA, et al: Coccidioidomycosis in HIV Infected Patients: Review of 83 Cases—Abstracts of the 1993 Infectious Diseases Society of America (IDSA) Annual Meeting. Clin Infect Dis 1993; 17:543, abstract No. 74

42. DiTomasso JP, Ampel NM, Sobonya RE, Bloom JW: Bronchoscopic diagnosis of pulmonary coccidioidomycosis: Comparison of cytology, culture and transbronchial biopsy. Diagn Microbiol Infect Dis; in press

43. Galgiani JN, Catanzaro A, Cloud GA, et al: Fluconazole therapy for coccidioidal meningitis. Ann Intern Med 1993; 119:28-35